

Remarks

A. Status of Claims/Amendments

Claim 21 has been amended. Claims 1-20 have been canceled as drawn to non-elected inventions. Claims 22 and 30-32 have been canceled as discussed below. Claim 34 has been added. Thus, claims 21, 23-29 and 33-34 are pending.

Support for new claim 34, which concerns the preparation of a pharmaceutical composition for intravenous, intramuscular or subcutaneous administration, can be found throughout the specification, including, for example, Figures 12-16; page 2, lines 14-15; page 6, lines 7-12; and pages 21-22, 35.

Claim 21 has been amended to introduce the subject matter of claims 22 and 30 with some slight differences (i.e., amended claim 21 does not require cooling to 'room' temperature). Also, the words "essentially spontaneously" has been added to clarify that the claim is directed to microemulsions as distinct from emulsions. Support for this amendment can be found on page 13, lines 6 – 17. We note also that amended claim 21 references "stirring" during the cooling. This stirring is typically what might be referred to as "gentle" stirring or gentle mixing.

Claims 31 and 32 have been canceled as drawn to non-elected species. Applicants reserve the right to refile a continuation directed generically to "molecules of interest".

Claim 33 has been reintroduced.

B. Novelty

The Action first rejects claims 21-23, 25, 27 and 30 as lacking novelty over the de Vringer publication. Applicants respectfully traverse on the basis that de Vringer is clearly concerned only with *emulsions*, whereas the claims at issue here are concerned with *microemulsions*.

Applicants are somewhat surprised at this rejection in that it retreads over ground addressed by the Applicants and conceded by the Examiner in a previous rejection. In the Response to Office Action Dated November 21, 2003, the Applicants presented irrefutable evidence that *emulsions* (as, for example, described in the art at issue in that action, U.S. Patent No. 5,658,575 ("Ribier")) was scientifically distinct from the *microemulsion* embraced by Claim 21. The Examiner apparently accepted this argument in withdrawing the rejection.

Claim 21 requires a method of making a nanoparticle that includes "making an oil-in water *microemulsion*." (emphasis added) The terms "microemulsion" and "emulsion" are clearly defined in the Specification, for example, on page 13, lines 6-17, state:

"...a "microemulsion" is a stable biphasic mixture of two immiscible liquids stabilized by a surfactant and usually a co-surfactant. Microemulsions are thermodynamically stable, isotropically clear, form spontaneously without excessive mixing, and have dispersed droplets in the range of about 5 nm to 140 nm. *In contrast*, emulsions are opaque mixtures of two immiscible liquids. Emulsions are thermodynamically unstable systems, and usually require the application of high-torque mechanical mixing or homogenization to produce dispersed droplets in the range of about 0.2 to 25 μm ." (emphasis added)

The de Vringer ('197) reference specifically states that it is concerned with emulsions (see, e.g., page 3, lines 18-23), and discloses an *emulsion* obtained when an oily phase and an aqueous phase are combined, heated, and *vigorously* stirred with a MICROFLUIDIZER® device at 10,000 PSI and/or a TURRAX® homogenizer at 2000 rpm. See Background of the Invention, page 2, lines 10-16; Summary of the Invention, page 2, lines 56-57; Detailed Description of the Invention, page 4 lines 34-46, and page 5 lines 22-24; Examples 1-7; Claims 15-17.

Indeed, de Vringer states that "vigorous" dispersion of the mixture – such as through the use of a high-shear homogenizer or microfluidizer – is "essential" to the preparation of the de Vringer emulsions. See page 4 lines 41-48. The various examples of emulsion preparations given by de Vringer provide further confirmation: When the de Vringer emulsion was subjected only to a 5 minute homogenization at 2000 rpm, the resultant emulsion was unstable. See de

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Vringer, Example 1, page 5, lines 54-56. However, when the emulsion was prepared in the same way, except that it was further subjected to microfluidization in a MICROFLUIDIZER® device at 10,000 PSI, the emulsion was stable. See de Vringer, page 6, lines 6-9. These statements demonstrate that, beyond question, de Vringer is concerned with emulsions, not microemulsions. Indeed, Applicants are unable to identify a single instance where de Vringer ('197) mentions or even hints at the preparation of "microemulsions" or a system that can be stably formed without vigorous mixing. If the Examiner is aware of any such disclosures in de Vringer, he is requested to point them out.

It is well known to those skilled in the art that emulsions and microemulsions are scientifically different compositions that have different physical and chemical properties. Remington's Pharmaceutical Sciences, 18th ed. (1990) is enclosed with this response, and it also provides information distinguishing emulsions from microemulsions.¹ For example, the beginning of page 271 of Remington states

Microemulsions are liquid dispersions of water and oil that are made homogeneous, transparent and stable by the addition of relatively large amounts of a surfactant and a cosurfactant...Microemulsions are intermediated in properties between micelles containing solubilized oils and emulsions. While emulsions are lyophobic and unstable, microemulsions are on the borderline between lyophobic and lyophilic colloids. True microemulsions are thermodynamically stable. Therefore, they are formed spontaneously when oil, water, surfactants, and cosurfactants are mixed together. The unstable emulsions require input of considerable mechanical energy for their preparation, which may be supplied by colloid mills, homogenizers or ultrasonic generators.

In that independent claim 21 and its dependent claims are concerned with microemulsions, not emulsions, the Action fails to set forth a *prima facie* case of anticipation of

¹ The Remington's reference is included for background information only. To the extent any of its descriptions conflict with those of the specification, the specification's descriptions should hold.

the rejected claims. For at least this reason, independent claim 21 and its dependent claims are clearly novel and patentably distinct over de Vringer.

C. Obviousness

The Action continues by rejecting the remaining claims, claims 24, 26 and 28-29, as obvious over the de Vringer publication. Applicants again respectfully traverse, and incorporate the comments above that point out the differences between emulsions and microemulsions. In light of the clear distinction between emulsions and microemulsions, there is no basis on the current record for making or maintaining a *prima facie* obviousness rejection of claims 24, 26 or 28-29.

D. New Claim 34 – Parenteral Compositions

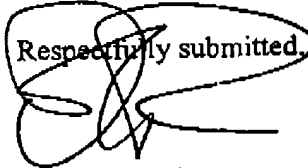
Applicants note that new claim 34 has been added, which is directed to subject matter even further removed from the teachings of de Vringer. Claim 34 concerns an additional step of formulating the nanoparticles prepared by the method of claim 21 into a pharmaceutical composition that is suitable for parenteral (e.g., intravenous, intramuscular, subcutaneous) administration. This is still further removed from the teachings of de Vringer, in that de Vringer is concerned solely with non-sterile, topical formulations that would be clearly contraindicated for parenteral administration, by virtue of its teaching of paraffin waxes, *etc.*, that would not be appropriate or acceptable for parenteral administration. There is no suggestion in de Vringer that Applicants have been able to identify that would teach or suggest nanoparticles that would be suitable for parenteral administration.

E. Conclusion

Applicant believes that this Submission fully responds to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn so the

claims may swiftly pass to issuance. Please contact the undersigned attorney at 512-536-3055 with any questions.

Respectfully submitted,



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Remington's Pharmaceutical Sciences

Eighteenth Edition

Pharmaceutical Sciences

1990

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Table IX—Micellar Solubilization Capacities of Different Surfactants for Estrone¹³

Surfactant	Concentration range, molarity	Temp. °C	Moles surfactant/mole solubilized estrone
Sodium laurate	0.025–0.023	40	91
Sodium oleate	0.002–0.35	40	53
Sodium lauryl sulfate	0.004–0.15	40	71
Sodium cholate	0.09–0.23	20	238
Sodium deoxycholate	0.007–0.36	20	476
Diamyl sodium sulfosuccinate	0.08–0.4	40	833
Dioctyl sodium sulfosuccinate	0.002–0.05	40	198
Tetradecyltrimethylammonium bromide	0.006–0.08	20	46
Hexadecylpyridinium chloride	0.001–0.1	20	32
Polyorbate 20	0.002–0.16	20	161
Polyorbate 60	0.0008–0.1	20	83

proportional to the overall surfactant concentration. Below the cmc, no solubilization takes place. This is represented by Curve E of Fig 19-17.

The second category of compounds to be solubilized are often liquid at room temperature and consist of relatively small, symmetrical, and/or flexible molecules such as many constituents of essential oils. These molecules mix and blend in freely with the hydrocarbon portions of the surfactants in the core of the micelles, so as to become indistinguishable from them. Such compounds are extensively solubilized and in the process usually swell the micelles: they augment the volume of the hydrocarbon core and increase the number of surfactant molecules per micelle. Their solubilization frequently lowers the cmc.

Microemulsions¹⁴⁻¹⁶

Microemulsions are liquid dispersions of water and oil that are made homogeneous, transparent, and stable by the addition of relatively large amounts of a surfactant and a cosurfactant. Oil is defined as a liquid of low polarity and low miscibility with water, eg, toluene, cyclohexane, mineral or vegetable oils.

Microemulsions are intermediate in properties between micelles containing solubilized oils and emulsions. While emulsions are lyophobic and unstable, microemulsions are on the borderline between lyophobic and lyophilic colloids. True microemulsions are thermodynamically stable.¹⁷ Therefore, they are formed spontaneously when oil, water, surfactants, and cosurfactants are mixed together. The unstable emulsions require input of considerable mechanical energy for their preparation, which may be supplied by colloid mills, homogenizers or ultrasonic generators.

Both emulsions and microemulsions may contain high volume fractions of the internal phase. For instance, some O/W systems contain 75% (v/v) of oil dispersed in 25% water, although lower internal phase volume fractions are more common.

At low surfactant concentrations, viz, low multiples of the cmc, micelles are spheres (Fig 19-18A, B and E) or ellipsoids. When an oil is solubilized by micelles in water, it blends into the micellar core formed by the hydrocarbon tails of the surfactant molecules (Fig 19-19) and swells the micelles.

Spherical or ellipsoidal micelles are nearly monodisperse, and their mean diameters are in the range of 25 to 60 Å. Microemulsion droplets also have a narrow droplet size distribution with a mean diameter range of approximately 60 to 1000 Å. Since the droplet diameters are less than $\frac{1}{4}$ of the wavelength of light (4200 Å for violet and 6600 Å for red

light), microemulsions scatter little light and are, therefore, transparent or at least translucent.

Emulsions have very broad droplet size distributions. Only the smallest droplets, with diameters of about 1000 to 2000 Å, are below the resolving power of the light microscope. The upper size limit is 25 or 50 μ m (250,000 or 500,000 Å). Because emulsion droplets are comparable in size, or larger, than the wavelength of visible light, they scatter it more or less strongly depending on the difference in refractive index between oil and water. Thus, most emulsions are opaque.

The three disperse systems—micellar solutions, microemulsions, and emulsions—can be of the O/W (oil-in-water) or W/O type. Aqueous micellar surfactant solutions can solubilize oils and lipid-soluble drugs in the core formed by their hydrocarbon chains. Likewise, oil-soluble surfactants like sorbitan monooleate and docosate sodium form "reverse micelles" in oils (Fig 19-18E) capable of solubilizing water in the polar center. The solubilized oil in the former micelles and the solubilized water in the latter may in turn enhance the micellar solubilization of oil-soluble and water-soluble drugs, respectively.

Oil-soluble drugs have been incorporated into O/W emulsions by dissolving them in the oil phase before emulsification.¹⁸ By the same token, it may be possible to dissolve oil-soluble drugs in a vegetable oil and make an oral or parenteral O/W microemulsion. The advantage of such microemulsion systems over conventional emulsions is their smaller droplet size and superior shelf stability. Aqueous micellar solutions¹⁹ and O/W microemulsions²⁰ have both been used as aqueous reaction media for oil-soluble compounds.

Emulsions and micellar solutions of oils solubilized in aqueous surfactant solutions consist of three components, oil, water and surfactant. Microemulsions generally require a fourth component, called cosurfactant. Commonly used cosurfactants are linear alcohols of medium chain length, which are sparingly miscible with water. Since the cosurfactants as well as the surfactants are surface-active, they promote the generation of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa, resulting in the formation of microemulsions. The large interfacial area between oil and water permits the extensive formation of a mixed interfacial film consisting of surfactant and cosurfactant. This film is called the "interphase" because it is thicker than the surfactant monolayers formed at oil-water interfaces in emulsions. The interfacial tension at the oil-water interface in microemulsions approaches zero, which also contributes to their spontaneous formation. According to another viewpoint, microemulsions are regarded as micelles extensively swollen by large amounts of solubilized oil.

Typical formulations for an O/W and a W/O microemulsion are shown in Table X. The ratio, g surfactant/g solubilized oil or water is in the range of 2 to 20 for micellar solutions and 0.01 to 0.1 for emulsions. Microemulsions have intermediate values: The ratios for the formulations in Table X are near unity. In industrial formulations,

Table X—Microemulsion Formulations

Compound	Function	Content in microemulsions, %	
		O/W	W/O
Sodium lauryl sulfate	Surfactant	13	10
1-Pentanol	Cosurfactant	8	25
Xylene	Oil	8	50
Water	—	71	15

Table XIX—Approximate HLB Values for a Number of Emulsifying Agents

Generic or chemical name	HLB
Sorbitan trioleate	1.8
Sorbitan tristearate	2.1
Propylene glycol monooleate	3.4
Sorbitan sesquileate	3.7
Glycerol monooleate (non self-emulsifying)	3.8
Sorbitan monooleate	4.8
Propylene glycol monolaurate	4.5
Sorbitan monolaurate	4.7
Glycerol monooleate (self-emulsifying)	5.6
Sorbitan monopalmitate	6.7
Sorbitan monolaurate	8.6
Polyoxyethylene-4-lauryl ether	9.5
Polyethylene glycol 400 monooleate	11.6
Polyoxyethylene-4-sorbitan monolaurate	13.8
Polyoxyethylene-20-sorbitan monooleate	15.0
Polyoxyethylene-20-sorbitan monopalmitate	15.6
Polyoxyethylene-20-sorbitan monolaurate	16.7
Polyoxyethylene-40-stearate	16.9
Sodium oleate	18.0
Sodium lauryl sulfate	40.0

emulsifier and emulsion type has been concerned with surface-active agents that form interfacial monolayers. The present discussion, therefore, will concentrate on this class of agents.

Hydrophile-Lipophile Balance—As the emulsifier becomes more hydrophilic, its solubility in water increases and the formation of an O/W emulsion is favored. Conversely, W/O emulsions are favored with the more lipophilic emulsifiers. This led to the concept that the type of emulsion is related to the balance between hydrophilic and lipophilic solution tendencies of the surface-active emulsifying agent.

Griffin⁵⁹ developed a scale based on the balance between these two opposing tendencies. This so-called *HLB scale* is a numerical scale, extending from 1 to approximately 50. The more hydrophilic surfactants have high HLB numbers (in excess of 10), while surfactants with HLB numbers from 1 to 10 are considered to be lipophilic. Surfactants with a proper balance in their hydrophilic and lipophilic affinities are effective emulsifying agents since they concentrate at the oil/water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table XV. Some commonly used emulsifiers and their HLB numbers are listed in Table XIX. The utility of the HLB system in rationalizing the choice of emulsifying agents when formulating an emulsion will be discussed in a later section.

Rate of Coalescence and Emulsion Type—Davies⁶⁰ indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially which contains oil dispersed in water and water dispersed in oil (Fig 19-38). The type of the final emulsion which results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed since the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

According to Davies, the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate 1} = C_1 e^{-W_1/RT} \quad (39)$$

The term C_1 is a collision factor which is directly proportional to the phase volume of the oil relative to the water, and is an inverse function of the viscosity of the continuous phase (water). W_1 defines an energy barrier made up of several contributing factors that must be overcome before coalescence can take place. First, it depends on the electrical potential of the dispersed oil droplets, since this affects repulsion. Second, with an O/W emulsion, the hydrated layer surrounding the polar portion of emulsifying agent must be broken down before coalescence can occur. This hydrated layer is probably around 10 Å thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Equation 40 describes the rate of coalescence of water globules dispersed in oil, namely

$$\text{Rate 2} = C_2 e^{-W_2/RT} \quad (40)$$

Here, the collision factor C_2 is a function of the water/oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier W_2 is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of $-\text{CH}_2-$ groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

Davies⁶⁰ showed that the HLB concept is related to the distribution characteristics of the emulsifying agent between the two immiscible phases. An emulsifier with an HLB of less than 7 will be preferentially soluble in the oil phase and will favor formation of a W/O emulsion. Surfactants with an HLB value in excess of 7 will be distributed in favor of the aqueous phase and will promote O/W emulsions.

Preparation of Emulsions

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

Selection of Emulsifying Agents

The selection of the emulsifying agent, or agents, is of prime importance in the successful formulation of an emulsion. In addition to its emulsifying properties, the pharmacist must ensure that the material chosen is nontoxic and that the taste, odor, and chemical stability are compatible with the product. Thus, an emulsifying agent which is entirely suitable for inclusion in a skin cream may be unacceptable in the formulation of an oral preparation due to its potential toxicity. This consideration is most important when formulating intravenous emulsions.

The HLB System—With the increasing number of available emulsifiers, particularly the nonionics, the selection of emulsifiers for a product was essentially a trial-and-error procedure. Fortunately, the work of Griffin^{59,60} provided a logical means of selecting emulsifying agents. Griffin's method, based on the balance between the hydrophilic and lipophilic portions of the emulsifying agent, is now widely used and has come to be known as the *HLB system*. It is used most in the rational selection of combinations of non-

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Table XX—Relationship between HLB Range and Surfactant Application

HLB range	Use
0-3	Antifoaming agents
4-8	W/O emulsifying agents
7-9	Wetting agents
8-18	O/W emulsifying agents
13-15	Detergents
10-18	Solubilizing agents

Table XXI—Required HLB Values for Some Common Emulsion Ingredients

Substance	W/O	O/W
Acid, stearic		17
Alcohol, cetyl		13
Labolin, anhydrous	8	15
Oil, cottonseed		7.5
mineral oil, light	4	10-12
mineral oil, heavy	4	10.5
Wax, beeswax	5	10-16
microcrystalline paraffin		9

ionic emulsifiers, and we shall limit our discussion accordingly.

As shown in Table XX, if an O/W emulsion is required, the formulator should use emulsifiers with an HLB in the range of 8-18. Emulsifiers with HLB values in the range of 4-6 are given consideration when a W/O emulsion is desired. Some typical examples are given in Table XIX.

Another factor is the presence or absence of any polarity in the material being emulsified, since this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values; i.e., the HLB value required by a particular material if it is to be emulsified effectively. Some values for oils and related materials are contained in Table XXI. Naturally, the required HLB value differs depending on whether the final emulsion is O/W or W/O.

Fundamental to the utility of the HLB concept is the fact that the HLB values are algebraically additive. Thus, by using a low HLB surfactant with one having a high HLB it is possible to prepare blends having HLB values intermediate between those of the two individual emulsifiers. Naturally, one should not use emulsifiers that are incompatible. The following formula should serve as an example.

O/W Emulsion	
Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Sorbitan monooleate (HLB 4.8)	
Polyoxyethylene 20 sorbitan monooleate (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Since the formula calls for 5 g, the required weights are 2.1 g and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase which is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole stirred continuously until cool.

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table XXII shows

Table XXII—Nonionic Blends having HLB Values of 10.5

Surfactant blend	HLB	Required amounts (%) to give HLB = 10.5
Sorbitan tristearate	3.1	34.4
Polyoxyethylene 20 sorbitan monooleate	14.9	65.6
Sorbitan monopalmitate	6.7	67.3
Polyoxyethylene 20 sorbitan monopalmitate	15.6	42.7
Sorbitan sesquileste	3.7	48.5
Polyoxyethylene lauryl ether	18.9	51.5

the various proportions required, using other pairs of emulsifying agents, to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

Occasionally, the required HLB of the oil may not be known, in which case it becomes necessary to determine this parameter. Various blends are prepared to give a wide range of HLB mixtures and emulsions are prepared in a standardized manner. The HLB of the blend used to emulsify the best product, selected on the basis of physical stability, is taken to be the required HLB of the oil. The experiment should be repeated using another combination of emulsifiers to confirm the value of the required HLB of the oil to within, say, ± 1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin⁵⁰ developed simple equations which can be used to obtain an estimate with certain compounds. It has been shown that the ability of a compound to spread at a surface is related to its HLB. In another approach a linear relation between HLB and the logarithm of the dielectric constant for a number of nonionic surfactants has been observed. An interesting approach has been developed by Davies⁵⁴ and is related to his studies on the relative rates of coalescence of O/W and W/O emulsions (page 304). According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table XXIII). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

Table XXIII—HLB Group Numbers⁵¹

	Group number
Hydrophilic groups	
—SO ₃ —Na ⁺	38.7
—COO—K ⁺	21.1
—COO—Na ⁺	19.1
N (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
—COOH	2.1
Hydroxyl (free)	1.9
—OH	1.3
Hydroxyl (sorbitan ring)	0.6
Lipophilic groups	
—CH—	
—CH ₂ —	
—CH ₂ —	
—CH ₂ —	-0.475
Derived groups	
—(CH ₂ —CH ₂ —O)—	+0.83
—(CH ₂ —CH ₂ —CH ₂ —O)—	-0.15

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tated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

Some spirits show incompatibilities characteristic of the ingredients they contain. For example, Aromatic Ammonia Spirit cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid-base reaction (ammonia-phosphate) occurs and, if the alcohol content of the final mixture is too low, codeine will precipitate.

Toothache Drops

Toothache drops are preparations used for temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Anesthet-

ic compounds include clove oil, eugenol or benzocaine; other ingredients include camphor, creosote, menthol and alcohol.

These preparations no longer are recognized officially. Furthermore, dentists do not recommend the use of toothache drops if the patient has ready access to adequate dental services. The preparations may damage the gums and produce complications more severe than the original toothache. However, many areas do not have adequate dental services, and the pharmacist will, of necessity, handle these preparations, and he should warn the patient of possible hazards associated with their use.

Toothache Drops NF XI contains 25 g of chlorobutanol and sufficient clove oil to make the product measure 100 mL. Another formulation contains creosote, clove oil, benzocaine and alcohol in a flexible colloid base.

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is critical, of course, and must be such that the system achieves maximum stability. However, even under the best conditions, separation of the two phases will occur unless a third substance, an *emulsifying agent*, is incorporated. The basic emulsion must, therefore, contain three components, but the products of commerce may consist of a number of therapeutic agents dissolved in either of the two phases.

Most emulsions incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. This broadening of the basic definition for the term *emulsion* is recognized in the USP.

An emulsion is a two-phase system in which one liquid is dispersed in the form of small droplets throughout another liquid. The dispersed liquid is known as the internal or discontinuous phase, whereas the disperser medium is known as the external or continuous phase. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion and can be diluted easily and uniformly with water. Conversely, where water, or an aqueous solution is the dispersed phase, and oil, or oleaginous material, is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion.

Many emulsifying agents (or emulsifiers) are available, among them the following:

Natural Emulsifying Agents—These substances may be derived from either animal or vegetable sources. Examples of those obtained from the former source are gelatin, egg yolk, casein, wool fat or cholesterol. Acacia, tragacanth, chondrus or pectin are representative of those obtained from vegetable sources. Various cellulose derivatives, eg, methylcellulose and carboxymethylcellulose, are used to increase the viscosity of the aqueous phase and thereby enhance emulsion stability.

Finely Divided Solids—Examples are bentonite, magnesium hydroxide, aluminum hydroxide or magnesium trisilicate.

Synthetic Emulsifying Agents—This group may be subdivided further into the anionic, cationic or nonionic agents. Examples are, in order of presentation, sodium lauryl sulfate, benzalkonium chloride or polyethylene glycol 400 monopalmitate.

Many of these emulsifying agents are described in greater detail in Chapter 66.

In NF XIII it was suggested that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gave specific directions for the preparation of emulsions using gelatin as an emulsifying agent. These preparations are based on either type A or type B gelatin.

Type A gelatin is prepared by acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended:

Gelatin (Type A)	8 g
Tartaric Acid	0.5 g
Flavor as desired	
Alcohol	60 mL
Oil	500 mL
Purified Water, to make	1000 mL

Add the gelatin and the tartaric acid to about 300 mL of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98° and maintain this temperature for about 20 min. Cool to 50°, add the flavor, the alcohol and sufficient purified water to make 600 mL. Add the oil, agitate the mixture thoroughly and pass it through a homogenizer or a colloid mill until the oil is dispersed completely and uniformly.

This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with other anionic emulsifying agents but is incompatible with cationic types. If the emulsion contains 50% oil, 5 g of Type B gelatin, 2.5 g of sodium bicarbonate and sufficient tragacanth or agar should be incorporated into the aqueous phase to yield 1000 mL of product of the required viscosity.

The emulsion type (O/W or W/O) is of lesser significance if the final preparation is to be applied to the skin. If there are no breaks in the skin, a W/O emulsion can be applied more evenly since the skin is covered with a thin film of sebum. The latter substance favors the oily phase and contributes to the ease of application. The choice of emulsion type will, however, depend on many other factors. This particularly is true for those preparations which have basic cosmetic characteristics. It may be advantageous to formulate an O/W emulsion if ease of removal is an important consideration to the patient.

An emulsion that may be prepared by the mortar and pestle method is the following Mineral Oil Emulsion USP.

Mineral Oil	500 mL
Acacia, in very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water, a sufficient quantity	1000 mL

The mineral oil and acacia are mixed in a dry Wedgwood mortar. Water (250 mL) is added and the mixture triturated vigorously until an emulsion is formed. A mixture of the syrup, 50 mL of purified water and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume, the mixture mixed well and homogenized.

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